REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)					
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FILL

Unit:

United States Patent 1191

Queen et al.

 $\Pi\Pi$ **Patent Number:**

5,693,762

Date of Patent: [45]

Dec. 2, 1997

[54] HUMANIZED IMMUNOGLOBULINS

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[21] Appl. No.: 487,200

[22] Filed: Jun. 7, 1995

Related U.S. Application Data

[63] Continuation of Scr. No. 634,278, Dec. 19, 1990, Pat. No. 5,530,101, which is a continuation-in-part of Scr. No. 590, 274, Sep. 28, 1990, abundoned, and Ser. No. 310,252, Feb. 13, 1989, abandoned, which is a continuation-in-part of Ser. No. 290,975, Dec. 28, 1988, abandoned.

U.S. Cl. 530/387.3; 530/388,22; 424/133.1; 424/143.1

[58] Field of Search 530/387.3, 388.22; 424/133.1, 143.1

[56] References Cited

U.S. PATENT DOCUMENTS

4,578,335	3/1986	Urdal et al	530/351
4,816,397	3/1989	Boss et al	435/68
4,816,565	3/1989	Honjo et al	43.469.1
4,816,567	3/1989	Cabilly et al	530/387
4,845,198		Urdal et al	
4,867,973		Goers et al	
5,198,359	3/1993	Taniguchi et al	435/252.3
5,225,539	7/1993	Winter	530/387.3
5,476,786	12/1995	Huston et al	435/252.33

FOREIGN PATENT DOCUMENTS

-		
0 120 694	10/1984	European Pat. Off
0171496	2/1986	European Pat. Off
0173494	3/1986	European Pat. Off
0184187	6/1986	European Pat. Off
0256654	7/1987	European Pat. Off
0 239 400	9/1987	European Pat. Off
0239400	9/1987	European Pat. Off
0266663	6/1988	European Pat. Off
0 323 806	7/1989	European Pat. Off
0 328 404	8/1989	European Pat. Off
0 365 209	4/1990	European Pat. Off
0 365 997	5/1990	European Pat. Off
0 125 023	6/1991	European Pat. Off
0460167	12/1991	European Pat. Off
2188941	10/1987	United Kingdom .
8928874	12/1989	United Kingdom .
VO 86/05513	9/1986	WIPO.
VO 87/02671	5/1987	WIPO.
VO 88/09344	12/1988	WIPO.
VO 89/01783	3/1989	WIPO.
91/09967	7/1991	WIPO.

OTHER PUBLICATIONS

"Groves et al. Hybridoma vol. 6 (1) 1987 71.

Chothia, C. and Lesk, A.M., "Canonical Structures for the 2 Hypervariable Regions of Immunoglobulins," J. Mol. Biol., .196:901–917 (1987).

Jones et al., "Replacing the complementarity-determining ?regions in a human antibody with those from a mouse. Nature, 321:522-525 (1986).

Lunghans et al., Cancer Res., 50:1495-1502 (1990).

Kupiec-Weglinski et al., Proc. Natl. Acad. Sci., 83:2624 (1986).

Maeda et al., "Construction of reshaped human antibodies 6 with HIV-neutralizing activity," Hum. Antibod. Hybrid., **2**:124–134 (1991).

Morrison et al., "Chimeric human antibody molecules: Mouse antigent binding-domains with human constant region domains," Proc. Natl. Acad. Sci., 81:6851-6859 (1984).

Morrison, S.L., "Transfectomas Provide Novel Chimeric Antibodies," Science, 229:1202-1207 (1985).

Neuberger et al., "A hapten-specific chimeric IgE antibody with human physiological effector function," Nature, 314:268-270 (1985).

Riechmann et al., "Reshaping human antibodies for (1988).

Sahagan et al., "A Genetically Engineered Murine/Human Chimeric Antibody Retains Specificity for Human Tumor-Associated Antigen," J. Immunol., 137:1066-1074

Verhoeyen et al., "Reshaping Human Antibodies: Grafting an Antilysozyme Activity," Science, 239:1534-1536 (1988). Amit et al., Science, 233, 747-753 (1986).

12 Cheetham, Protein Engineering, 2(3), 170–172 (1988).

(List continued on next page.)

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[57] **AB°TRACT**

Novel methods for producing, and compositions of, humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin are provided. Bach humanized immunoglobulin chain will usually comprise, in addition to the CDR's, amino acids from the donor immunoglobulin framework that are, e.g., capable of interacting with the CDR's to effect binding affinity, such as one or more amino acids which are immediately adjacent to a CDR in the donor immunoglobulin or those within about about 3 Å as predicted by molecular modeling. The heavy and light chains may each be designed by using any one or all of various position criteria. When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen, such as a protein or other compound containing an epitope.

20 Claims, 55 Drawing Sheets

OTHER PUBLICATIONS

Chothia et al., J. Mol. Biol., 186, 651-663 (1985).

Chothia et al., Nature, 342, 877-883 (1989).

17 Chothia et al., Science, 233, 755-758 (1986).

Chothia and Lesk, EMBO J., 5, 823-826 (1986).

19_Colman et al., Nature, 326, 358-362 (1987).

Davies et al., Ann. Rev. Immunol., 1, 87-117 (1983).

2/ Davies et al., J. Biol. Chem., 263(22), 10541-10544 (1988)./

22 Epp et al., Bur. J. Biochem., 45, 513-524 (1974).

23 Peldmann et al., Mol. Immunol., 18, 683-698 (1981).

Kabat, J. Immunol., 125, 961-969 (1980).

25 Lesk and Chothia, J. Mol. Biol., 160, 325-342 (1982).

Padlan, Mol. Immunol., 31, 169-217 (1994).

22 Palm et al., Hoppe Seyler's Z. Physiol. Chem., 354(12), 1651-1654 (1973).

Palm et al., Hoppe Seyler's Z. Physiol. Chem., 356, 167-191 (1975).

Panka et al., PNAS-USA, 85, 3080-3084 (1988).

30 Roberts et al., Nature, 328, 731-734 (1987).

J__Saul et al., J. Biol. Chem., 253(2), 585-597 (1978).

32 Sheriff et al., PNAS-USA, 84, 8075-8079 (1987).

32 Stanford and Wu, J. Theor. Biol., 88, 421-439 (1981).
34 Tramontano et al., J. Mol. Biol., 215, 175-182 (1990).

35 Verhoeyen et al., BioEssays, 8(2), 74-78 (1988).

34 Waldmann et al., Cancer Research, 45, 4559s-4562s (1985).

3.7 Wu and Kabat, J. Exp. Med., 132, 211-250 (1970).

Better et al. "Escherichia coli Secretion of an Active Chimeric Antibody Fragment," Science, 240:1041-1043 (1988).

Bird et al., "Single-Chain Antigen-Binding Proteins," Science, 242:423-426 (1988).

Boulianne et al., "Production of functional chimeric mouse/human antibody," *Nature*, 312:643-646 (1984).

Carter et al., "Humanization of an anti-p185^{HER2} antibody for human cancer therapy," *Proc. Natl. Acad. Sci.*, 89:4285-4289 (1992).

Co et al., "Humanized antibodies for antiviral therapy," Proc. Natl. Acad. Sci., 88:2869-2873 (1991).

Co et al., "Chimeric and humanized antibodies with specificity for the CD33 antigen," J. Immunol., 148:1149–1154 (1992).

Daugherty et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting, and rapid expansion of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins," Nuc. Acids. Res., 19:2471-2476 (1991).

Ellison et al., "The nucleotide sequence of a human inimunoglobulin c(gamma), gene," Nucleic Acids Res., 10:4071-(1982).

Farrar, J., "The biochemistry, biology, and the role of interleukin-2 in the induction of cytotoxic T cell and anti-body-forming B cell receptors," *Immunol. Rev.*, 63:129-166 (1982).

Poote et al., "Antibody framework residues affecting the Sconformation of hypervariable loops," J. Mol. Biol., (224:487-499 (1992).

Gorman et al., "Reshaping a therapeutic CD4 antibody," Proc. Natl. Acad. Sci., 88:4181-4185 (1991).

Greene et al., "Growth of Human T Lymphocytes: An Analysis of Interleukin 2 and its Cellular receptor," Progress in Hematology XIV, E. Brown, ed., Grune and Statton, New York, pp. 283-301 (1986).

Hale et al., "Remission Induction in Non-Hodgkin Lymphoma with Reshaped Human Monoclonal Antibody CAMPATH-1H," Lancet, Dec. 17, 1988, pp. 1394-1399.

Hieter et al., "Cloned Human and Mouse Kappa Immunoglobulin Constant and J. Region Genes Conserve Homology in Functional Segments," Cell, 22:197-207 (1980).

Huston et al., "Protein engineering of antibody binding sites: Recovery of specific activity in an anti-digoxin single-chain Pv analogue produced in Escherichia coli," Proc. Nat. Acad. Sci. USA, 85:5879-5883 (1988), Progress in Hematology XIV, B. Brown, ed., Grune and Statton, New York, p. 283,—(1986).

Kettleborough et al., "Humanization of a mouse monoclonal antibody by CDR-grafting: the importance of framework residues on loop conformation," *Protein Eng.*, 4:773-783 (1991).

Kirkman et al., J. Exp. Med., 162:358 (1985).

Leonard et al., "The human receptor for T-cell growth factor," J. Biol. Chem., 260:1872-1880 (1985).

Liu et al., "Expression of mouse::human immunoglobulin heavy-chain cDNA in lymphoid cells," Gene, 54:33-40 (1987).

Queen et al., "A humanized antibody that binds to the interleukin 2 receptor," Proc. Natl. Acad. Sci., 86:10029-10033 (1989).

Routledge et al., "A humanized monovalent CD3 antibody which can activate homologous complement," Eur. J. Immunol., 21:2717–2725 (1991).

Shalaby et al., "Development of humanized bispecific antibodies reactive with cytotoxic lymphocytes and tumor cells overexpressing the HER2 protooncogene," J. Exp. Med., 175:217-225 (1992).

Sharon et al., "Expression of a $V_H C_K$ chimaeric protein in mouse myeloma cells," *Nature*, 309:364-367 (1984).

Shearman et al., "Construction, expression and characterization of humanized antibodies directed against the human α/β T cell receptor," J. Immunol., 147:4366-4373 (1991).

Takeda et al., "Construction of chimaeric processed immu-Jooglobulin genes containing mouse variable and human constant region sequences," *Nature*, 314:452-454 (1985).

Tan et al., "A Human-Mouse Chimeric Immunoglobulin Gy Gene with a Human Variable Region is Expressed in Mouse Myeloma Cells," J. Immunol., 135:3564-3567 (1985).

Tempest et al., "Reshaping a human monoclonal antibody to inhibit human respiratory syncytial virus infection in vivo," Bio/Technology, 9:26-271 (1991).

Uchiyama et al., "A monoclonal antibody (anti-Tac) reactive with activated and functionally mature human T-cells,"

J. Immunol., 126:1393-1397 (1981).

Vitteta et al., "Redesigning nature's Poisons to Create Anti-Tumor reagents," Science, 238:1098-1104 (1987).

Waldmann, T.A., "The Structure, Function, and Expression of Interleukin-2 Receptors on Normal and Malignant Lymphocytes," Science, 232:727-732 (1986).

Woodle et al., "Humanized OKT3 antibodies: successful transfer of immune modulating properties and idiotype expression," J. Immunol., 148:2756–2763 (1992).

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